products in generic terms, as required by the Examiner. None of the amendments made herein constitutes the addition of new matter.

The Substitute Specification

Because the inadvertent obvious typographical and clerical errors and the changes requested by the Examiner are so numerous, Applicants have provided a substitute specification (excluding the claims pages) which incorporates these changes. None of these amendments constitutes the addition of new matter.

The Objection to the Specification

The Examiner has requested that the Specification be amended to provide generic language related to such trademarked items as "RNAZOL". Applicants have endeavored to comply with the request of the Examiner.

Applicants respectfully note that the TRITON X100 and other trademarks have been capitalized, and descriptions were provided for RNAzol B and RNAeasy. Applicants have now further amended the Specification to use capital letters and to supply the generic terminology where possible. A search of the United States Patent and Trademark Office's online trademark database did not uncover references to TUNEL or NONIDET which appeared to be relevant to the present technology. TUNEL is an acronym for the technique known as Terminal deoxyynucleotidyl transferase-mediated Transferase dUTP Nick End Labeling.

In view of the foregoing, Applicants respectfully request withdrawal of the objection to the Specification.

Claim Objections

Claim 15 has been amended to claim dependency from claim 11. It is believed that the present amendment to claim 15 makes this objection moot.

The Rejections under 35 U.S.C. 103(a)

Claims 11-12, 14-17 and 19-23 have been rejected under 35 U.S.C. 103(a) as allegedly obvious over United States Patent No. 5,763,416 ('416) or WO 96/39431 in view of United States Patent No. 4,654,084 ('084), United States Patent No. 5,700,774 ('774) and United States Patent No. 6,048,964. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the '416 patent or WO 96/39431 teaches a method for producing cultured or bone marrow stromal cells for implantation at the site of a bone infirmity by transforming with recombinant bone morphogenic protein (BMP). The '416 patent is alleged to suggest the use of PTH in the method, where a BMP and PTH can be co-expressed in the target cells and identifies the requirement of BMP and/or PTH receptors in the target cells as well as suggesting the use of progenitor cells. WO 96/39431 taught BMP-10; '416 taught the use of BMP-2 or other BMPs. The '084 patent is said to teach that BMP-2 is closely related to BMP-10, where BMP-2 and BMP-10 may be used interchangeably in a method for use for treating a bone infirmity. The '774 patent is said to teach the interchangeability of BMP-2 and BMP-10, as well as the use of PTH and PTH receptors n cells in need of treatment with BMP-2, where the affected bone-generating target cells are known to express the PTH receptor. The '964 patent is said to teach that recombinant DNA sequences were used to produce BMP-2 in cells and that BMP-2 is known to produce differentiation and proliferation of bone progenitor cells.

The Patent Office has maintained that the use of BMP-2 is obvious. Applicants respectfully note that the use of BMP-2 has advantages which the Patent Office has not noted to be associated with BMP-10 or other bone morphogenic proteins. For example, the Specification at page 47, lines 9-13 indicates that apoptosis appeared to be less in cells transfected with an adenovirus vector encoding BMP-2 than in control cells. The Patent Office has not indicated this observation with BMP-10 or other BMPs. The present application also teaches a positive effect on differentiation and on proliferation (see page 48, lines 21-23) of BMP-2, again expressed via an adenovirus vector. Again, the Patent Office has not pointed to these effects of BMP-2 as compared with other BMPs. The Patent Office has countered that the Specification teaches that

apoptosis decreases with time, and that the reduction in apoptosis is an expected result of induction of proliferation and differentiation.

Furthermore, Applicants have provided the Declaration of Debra Pittman which addresses the negative effects of BMP-10 when recombinantly expressed in vivo, after administration of recombinant adenovirus. No negative effects were observed in parallel experiments carried out with such an adenovirus which directed the expression of BMP-2.

Applicants also respectfully submit a copy of a publication by Moutsatsos et al. entitled "Exogenously Regulated Stem Cell-Mediated Gene Therapy for Bone Regeneration", which appeared in the April 2001 issue of Molecular Therapy (volume 3, issue no. 4, pages 449-461. This reference appeared in a refereed scientific journal. Applicants request that the Examiner consider this publication as further evidence of the nonobviousness of the present invention.

The Patent Office has responded that it would also have been obvious that BMP-2 had a positive effect on differentiation and proliferation. The Patent Office has stated that it would have been expected based on the cited prior art. Additionally, the Patent Office has not accepted Applicants' statement that the present invention provided unexpectedly improved results over the prior art.

Applicants respectfully submit that at most it would have been obvious to try the methods of the present invention as now claimed, and that the data obtained reflect unexpectedly improved results for BMP-2.

In addition, there must be a reasonable probability of success provided by the cited references (see, e.g., In re O'Farrell, 7 U.S.P.Q.2d 1673 C.A.F.C, 1988). There is nothing in these references which indicate that the methods and compositions of the present inventors would be successful or that the results would be so dramatically different with BMP-2 as compared with BMP-10.

With respect to the alleged interchangeability of the BMP-2 and BMP-10, Applicants respectfully submit a Declaration under 37 C.F.R. 1.132 executed by Debra Pittman. Pittman's Declaration describes experiments in which recombinant adenoviruses were introduced by the intravenous route or the subcutaneous route. Parallel experiments were carried out with such adenoviruses directing the expression of BMP-2 or BMP-10. The results described in the Declaration show that there are deleterious effects associated with the administration of adenoviruses expressing BMP-10. Because the results observed with BMP-2 were not the same as those observed with BMP-10, one must conclude that these two BMPs are **not** functionally equivalent in their biological activities in vivo and therefore, these two BMPs are not interchangeable.

In view of the information submitted relative to the biological activities of BMP-2 and BMP-10, Applicants respectfully maintain that the teachings of the WO 96/39431; 4,654,084; and 5,700,774 patent documents do not contribute to a proper prima facie case of obvious, and the withdrawal of the rejections under 35 U.S.C. 103(a) based on these references should be withdrawn.

In view of the foregoing arguments and the Declaration of Debra Pittman, Applicants respectfully maintain that the present invention as claimed is not *prima facie* obvious the cited references, and the withdrawal of this rejection is respectfully requested.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (two months) and a check in the amount of $400.00 as required by 37 C.F.R. 1.17. It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

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